Is protection by inhalation agents volatile? Controversies in cardioprotection

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"I would have everie man write what he knowes and no more."–Montaigne

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Editorial I

Is protection by inhalation agents volatile? Controversies in cardioprotection

The old Latin saying *'nomen est omen'* suggests that a name is indicative of, or notorious for, its true but hidden nature. Likewise, current clinical evidence on organ protection elicited by ether-derived inhalation agents ('anaesthetic preconditioning') appears volatile or, to say the least, not fully convincing. In this issue of the *British Journal of Anaesthesia*, Piriou and colleagues[1] report on sevoflurane preconditioning in patients undergoing on-pump coronary artery bypass graft (CABG) surgery. Despite some postoperative functional improvement, the primary outcome measure troponin I and some molecular markers of an effective preconditioning process in the heart remained unaffected. These rather disappointing results conflict, at least in part, with previous more promising clinical reports[2–6] and call for clarification.

Motivated by the work of Verdouw and colleagues[7] and Reimer and colleagues,[8] Murry and colleagues[9] described for the first time in 1986 the phenomenon termed 'ischaemic preconditioning' in canine myocardium. Since then, this potent endogenous protective mechanism has been confirmed in almost all species, including man.[10 11] A few years later, in 1993, late preconditioning, which reflects a second delayed window of protection occurring 12–96 h after initiation of preconditioning, was described.[12 13] This second window of protection is the result of transcriptional reprogramming, depending on *de novo* protein synthesis and is of particular clinical relevance, as it is nearly 30 times longer than the first window, which lasts for only 2–3 h. Today, we know that cardiac preconditioning can be elicited more safely by pharmacological means than by brief ischaemic hits. This is of particular relevance for the already jeopardized diseased heart. Two anaesthesia research groups independently reported the preconditioning-mimicking effects of isoflurane in 1997,[14 15] and isoflurane-induced delayed protection was first reported in 2003 in a rabbit model.[16] Recently, molecular evidence of delayed preconditioning after sevoflurane inhalation even at sub-anaesthetic concentrations (<0.5 MAC) was also reported in humans.[17] Extensive experimental work aimed at elucidating the complex signalling cascade involved in anaesthetic-induced preconditioning has so far deciphered many, but not all, of the underlying mysteries of tissue protection by ether-derived inhalation agents.[10 11 18] Unlike most other preconditioning-inducing agents, which must be administered directly into the coronary arteries to be effective without serious side-effects, ether-derived agents can be safely inhaled and thus act systemically providing total body protection.

In sharp contrast to the striking overwhelming evidence of cardioprotection by ether-derived inhalation agents in the experimental setting, are the results from predominantly smaller clinical studies. Meta-analyses evaluating ether-derived inhalation agent protection in patients undergoing CABG surgery recently concluded that there is only some protection with respect to cardiac function and troponin release but no evidence of reduced risk of myocardial infarction or cardiovascular mortality.[19 20] Although the proof of concept for anaesthetic preconditioning was demonstrated in on-pump CABG patients[4] in a placebo-controlled randomized trial, many questions with respect to the optimal protective protocol still need to be answered. Julier and colleagues,[4] as opposed to Piriou and colleagues,[1] used a rather higher sevoflurane concentration (4 vol.% corresponding to ~2 MAC) given for 10 min with a vaporizer attached to the cardiopulmonary bypass circuit. As with Piriou's findings, this study showed improved cardiac function, as determined by reduced perioperative plasma NT-proBNP levels, and for the first time translocation of protein kinase C (a key molecular mechanism in preconditioning) in human myocardium in response to sevoflurane, but no perioperative reduction in cardiac necrosis markers. Conversely, other studies have reported a significant decrease in myocardial necrosis markers in patients undergoing on-pump CABG[2 3] and more recently aortic valve surgery[21] if sevoflurane or desflurane was used throughout surgery. Other groups recently reported similar results.[5 6 22]

Data from animal studies investigating volatile anaesthetic-induced cardiac protection can help to explain these varying clinical findings only to a limited extent. First, laboratory work provides evidence that the early window of protection elicited by anaesthetic preconditioning exhibits a dose–response with a ceiling effect at 2 MAC,[23] and multiple cycles of anaesthetic wash-in/out were found to be more protective.[24] In clinical practice, anaesthetics are titrated to the degree of surgical stimulation mimicking multiple cycles of preconditioning. However, surgical stimulation does not necessarily reflect the extent, the intensity, and the duration of deleterious ischaemic episodes, rendering titration of protective levels of volatile anaesthetics a difficult task. Secondly, since desflurane enhances the release of catecholamines in the heart,[25] which activate supplemental protective signal transduction pathways, one might expect desflurane to be more protective than other agents.[26] On the other hand, an increased incidence of atrial fibrillation in patients anaesthetized with desflurane undergoing on-pump CABG surgery has been described.[2] Thirdly, the length of administration appears less important in laboratory animals, since exposures as short as 4 min were found to protect guinea pig hearts against ischaemia–reperfusion damage.[27] However, in the clinical arena, the combined pre- ('anaesthetic preconditioning') and post-ischaemic ('anaesthetic postconditioning') administration of potent inhalation agents ('anaesthetic conditioning') appears to be most protective.[3 28 29] Lastly, and most important, the preponderance of experimental work evaluating ethers as protective agents, with the exception of a few studies,[30 31] was conducted in healthy young hearts virtually ignoring the profound impact of metabolic (diabetes, hyperlipidaemia), structural (hypertrophy, remodelling after infarction), and age-related inhibitory effects on cardioprotection. This is a clear limitation of most laboratory animal studies. In the clinical setting, many confounding variables potentially enhance [opioids, nitroglycerin, sildenafil, statins, cardiopulmonary bypass *per se*, or blood pressure cuffs ('remote' ischaemic preconditioning)], annihilate, or even reverse (anti-preconditioning anaesthetics, sulfonylurea drugs, COX-2 inhibitors, non-steroidal anti-inflammatory drugs) ether-derived inhalation agent cardioprotection.[11] In view of this complex interplay, detailed reporting on possible confounding factors is essential in clinical studies. Perioperatively used opioids can effectively induce early and delayed preconditioning via μ-, δ-, and κ-opioid receptors, as shown in the study by Li and colleagues[32] in this issue of the *British Journal of Anaesthesia* and other previous reports.[33] So far, beta-blockers have not been found to inhibit anaesthetic protection, at least in the clinical setting.[1–6 21 22 29] NO-releasing beta-blockers such as nipradilol or nebivolol are capable of eliciting preconditioning.[11] Moreover, previous studies did not sufficiently evaluate the impact of various surgical techniques, the number of surgeons, and patient-specific genetic profile on anaesthetic organ protection. Single nucleotide polymorphisms ('genetic background') related to G-protein coupled receptors or downstream signalling targets may prove to be relevant for inhalation agent heart protection. Also, future clinical studies in the field should separate intrinsic (genetic) from extrinsic (environmental) factors modulating cardioprotection. The significance of transcriptional background activity in cardioprotection is supported by recent findings showing that anaesthetic-induced and constitutive gene regulatory control of myocardial substrate metabolism predicts postoperative cardiac function in patients undergoing CABG surgery.[29]

Piriou's study,[1] although not placebo-controlled, is clearly an important contribution to our current knowledge of anaesthetic protection in the heart. Such studies are necessary to identify the right target patients, who clearly benefit most from the treatment, and to refine the protective anaesthetic protocols. Piriou's study also highlights the need to objectify for 'cardioprotection' at the functional and biomarker level, such as pulmonary artery catheter measurements, echocardiography, and cardiac enzymes and hormones, as cardiac necrosis may be prevented by optimal cardioplegia, but postoperative cardiac dysfunction (stunning) may still occur and be receptive to protection.[1 4 22] Conversely, determination of tissue enzyme activity, consistent with an effective preconditioning process at the molecular level, is difficult in human specimens because of limitations, such as significant time delay during collection and mechanical manipulation, and thus may be less reliable. Most importantly, the assessment of 'outcome' in future preconditioning studies should not be confined to the immediate perioperative period but should include long-term cardiovascular evaluation.[34] Data from patients with acute coronary syndrome and myocardial infarction suggest that pre-infarct angina, a correlate of ischaemic preconditioning, can markedly improve long-term survival. Similarly, pharmacological preconditioning, which profoundly diminishes the perioperative inflammatory response, including high-sensitivity C-reactive protein and pregnancy-associated plasma protein A release,[29] may prevent coronary plaque ruptures and slow the progression of coronary occlusion (statin-like effects), thereby reducing the incidence of mid- and long-term cardiovascular complications.[34]

In this issue of the *British Journal of Anaesthesia*, Walsh and colleagues[35] review the current literature on remote ischaemic preconditioning, a fascinating alternative strategy to provide whole body protection. The intriguing concept of solvent transferable humoral triggers protecting at a distance was first observed in a rat heart model where a close correlation between area at risk and infarct size was exclusively observed in preconditioned-protected but not unprotected hearts, implying the presence of a protective agent acting at remote, that is intra- and inter-organ sites. Remote ischaemic and anaesthetic preconditioning share many signalling steps. However,

important disparities remain. First, interrupting blood flow by cross-clamping or blood pressure cuffs harbours the risk of thrombosis, plaque rupture, and embolization. Secondly, the right dose of ischaemia as the preconditioning trigger is less well controlled than the monitored application of volatile anaesthetics. Thirdly, experimental and clinical studies provide evidence that aged and diseased hearts may become resistant to ischaemic but much less to pharmacological preconditioning.[36] Finally, it remains elusive whether (remote) ischaemic and pharmacological preconditioning act synergistically or antagonize each other. Yet, nicorandil, a preconditioning-mimicking drug, was previously reported to inhibit ischaemic preconditioning.[11]

In summary, many experimental studies support the concept that ether-derived inhalation agents provide strong protection against ischaemia–reperfusion injury in the heart and other vital organs. Under clinical conditions, with many confounding variables, inhalation protection may appear 'volatile'. However, this protection is safe and devoid of the thread of further destabilizing inflamed plaques, as potentially may occur in ischaemic preconditioning. A recent landmark article discussing the need for translation of basic science into clinical practice proposes inhalation agents as readily available model drugs to successfully reproduce cardioprotection in clinical practice.[37] The work by Piriou and colleagues is a further step into this direction. Clearly, future experimental studies and larger-scale clinical trials are needed to discover all the cytoprotective secrets of Morton's ether sponge!

Declaration of Interest

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Editorial II

Confidential enquiries into anaesthetic deaths

The purpose of confidential enquiries into anaesthetic deaths has been to identify the cause of death and find areas of substandard care that might be amenable to correction. The enquiries with which anaesthetists in the UK have been most familiar with are the Confidential Enquiries into Maternal Deaths (CEMD), the Confidential Enquiries into Stillbirths and Deaths in Infancy (CESDI), and the National Confidential Enquiries into Perioperative Deaths (NCEPOD, now an acronym for National Confidential Enquiries into Perioperative Outcomes and Death). There is also a Confidential Enquiry into suicides and homicides. The organizations of CEMD and CESDI were taken over in 2003 by the Confidential Enquiries into Maternal and Child Health (CEMACH) which additionally has the role of looking at health issues related to these groups.

Repeated audits of deaths have a monitoring role as to whether the number of deaths are increasing or decreasing and whether new or different causes of death assume prominence with a need to address the cause.

CEMD has been producing triennial reports since 1952 classifying deaths directly due to pregnancy according to cause, such as haemorrhage, hypertensive diseases, thromboembolism, anaesthesia, etc. Achieving this level of information requires a detailed report on each death and interpretation by a series of assessors. The report celebrating 50 yr of these enquiries gives a potted history of